

UCLA

UCLA Previously Published Works

Title

Treating Opioid Dependence With Injectable Extended-Release Naltrexone (XR-NTX): Who Will Respond?

Permalink

<https://escholarship.org/uc/item/3gp3g2t2>

Journal

Journal of addiction medicine, 9(3)

ISSN

1932-0620

Authors

Nunes, Edward V
Krupitsky, Evgeny
Ling, Walter
et al.

Publication Date

2015-05-01

DOI

10.1097/adm.0000000000000125

Peer reviewed

Treating Opioid Dependence With Injectable Extended-Release Naltrexone (XR-NTX)

Who Will Respond?

Edward V. Nunes, MD, Evgeny Krupitsky, MD, PhD, Walter Ling, MD, Jacqueline Zummo, MPH, MBA, Asli Memisoglu, ScD, Bernard L. Silverman, MD, and David R. Gastfriend, MD

Objectives: Once-monthly intramuscular extended-release naltrexone (XR-NTX) has demonstrated efficacy for the prevention of relapse in opioid dependence, providing an alternative to agonist or partial agonist maintenance (ie, methadone and buprenorphine). The question remains, for whom is this unique treatment most efficacious and can patient-treatment matching factors be identified?

Methods: A moderator analysis was conducted on a previously reported 24-week, placebo-controlled, multisite, randomized controlled trial of XR-NTX ($n = 126$) versus placebo ($n = 124$) among recently detoxified opioid-dependent adults in Russia, which showed XR-NTX superior to placebo in proportion of opioid abstinent weeks. The moderator analysis examined a dichotomous indicator of good clinical response—achieving at least 90% of weeks abstinent over the

24-week trial. A series of logistic regression models were fit for this outcome as functions of treatment (XR-NTX vs placebo), each baseline moderator variable, and their interactions. The 25 baseline variables included demographics, clinical severity (Addiction Severity Index, SF-36, and Clinical Global Impression-Severity), functioning (EQ-5D), craving, and HIV serostatus (HIV+).

Results: More XR-NTX patients achieved 90% abstinence (64/126, 51%) versus placebo (39/124, 31%; $P = 0.002$). There were no significant interactions between baseline variables and treatment. There was a significant main effect of Clinical Global Impression-Severity score ($P = 0.02$), such that higher severity score was associated with a lower rate of Good Clinical Response.

Conclusions: The absence of significant baseline by treatment interactions indicates that no patient-treatment matching variables could be identified. This suggests that XR-NTX was effective in promoting abstinence from opioids across a range of demographic and severity characteristics.

Key Words: abstinence, clinical severity, extended-release naltrexone, opioid dependence, predictors

(*J Addict Med* 2015;9: 238–243)

From the New York State Psychiatric Institute and Department of Psychiatry (EVN), Columbia University, New York, NY; Bekhterev Research Psychoneurological Institute and St Petersburg State Pavlov Medical University (EK), Russia; Department of Psychiatry and Biobehavioral Sciences (WL), University of California, Los Angeles, CA; Alkermes, Inc (JZ, AM, BLS), Waltham, MA; and Treatment Research Institute (DRG), Philadelphia, PA.

Received for publication July 10, 2014; accepted January 20, 2015.

Supported by Alkermes, Inc, Dr Nunes was a member of the Advisory Board to Alkermes that designed this trial and served as a consultant to an expert panel convened by Alkermes. Dr Krupitsky is a consultant for Alkermes and received research funding for this study from Alkermes. Dr Ling has been an advisory board member for Alkermes and US World Med, has received research funding from Titan Pharmaceuticals, investigator initiated research funding from Hythiam, and research support, an unrestricted educational grant, and speaker support from Reckitt Benckiser. Drs Memisoglu and Silverman are full-time employees of Alkermes. Dr Gastfriend was an employee of Alkermes at the time of this research.

The Medisorb preparation used in XR-NTX (Vivitrol) was developed by Alkermes with support from the National Institute on Drug Abuse (grant R43DA013531) and the National Institute on Alcohol Abuse and Alcoholism (grant N43AA001002).

The authors declare no conflicts of interest.

Send correspondence and reprint requests to Bernard L. Silverman, MD, Clinical Science, Alkermes, Inc, 852 Winter St, Waltham, MA 02451. E-mail: bernard.silverman@alkermes.com.

Copyright © 2015 American Society of Addiction Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 3.0 License, where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially.

ISSN: 1932-0620/15/0903-0238

DOI: 10.1097/ADM.0000000000000125

Opioid dependence is a serious public health problem throughout the world, responsible for substantial morbidity, mortality (Stotts et al., 2009), and social costs (Birnbaum et al., 2011). Maintenance treatment with the opioid agonist methadone, and the partial agonist buprenorphine, has proved to be highly effective across multiple clinical trials (Mattick et al., 2003; Mattick et al., 2009) at reducing opioid use, improving social functioning, reducing criminal involvement, and infectious disease transmission in opioid-dependent patients. However, not all patients treated with methadone or buprenorphine respond well, and many opioid-dependent individuals avoid these treatments due to such factors as stigma, poor response in a prior treatment episode, fear of physical withdrawal upon treatment cessation, or patient preferences. The result is that, even in geographic regions where methadone and buprenorphine are readily available, a large proportion of opioid-dependent patients are not engaged in treatment or provided pharmacotherapy. Furthermore, there are regions of the United States, and countries around the

world, where methadone and buprenorphine are not legally available or readily accessible (International Harm Reduction Association, 2010; Krupitsky et al., 2010).

Naltrexone is a high-affinity opioid receptor antagonist, which produces potent blockade of the effects of opioids. However, until recently naltrexone was available only in daily pill form, and its effectiveness in practical terms was severely limited by poor adherence. It is easy for patients to stop the medicine (there are no withdrawal effects), and once blockade wears off, relapse becomes likely. The last decade has seen the development of several versions of long-acting injectable (Comer et al., 2006; Krupitsky et al., 2011) and implantable (Reece, 2007; Lobmaier et al., 2008; Mattick et al., 2009; Krupitsky and Blokhina, 2010) formulations of naltrexone, which has demonstrated efficacy in controlled clinical trials. Long-acting formulations circumvent problems with daily pill adherence and have produced treatment retention rates in clinical trials (Substance Abuse and Mental Health Services Administration, 2012) and posttreatment safety records (Hulse et al., 2009) that resemble those observed for buprenorphine and methadone.

Once-monthly intramuscular extended-release naltrexone (XR-NTX, Vivitrol; Alkermes, Inc, Waltham, MA) has thus emerged as a viable alternative to methadone and buprenorphine (Gastfriend, 2011), broadening the treatment options for opioid-dependent patients and for communities and treatment systems seeking to address this pandemic. This naturally raises the question—what types of patients are most likely to respond well to XR-NTX? The failure of oral naltrexone in placebo-controlled trials (Kirchmayer et al., 2003; Johansson et al., 2006; Minozzi et al., 2011) and the hypothesis that opioid-dependent patients suffer from an underactive endogenous opioid system that might be worsened by an antagonist (Goldstein, 1991) have raised concerns that naltrexone may be a niche treatment useful for only a narrow segment of the opioid-dependent population, for example, health professionals in monitored recovery programs. Previous research suggested that oral naltrexone may be less successful among opioid-dependent patients who have a history of methadone use (Sullivan et al., 2006), greater physiological dependence on opioids (higher daily opioid intake) (Sullivan et al., 2007; Carpenter et al., 2009), depression (Sullivan et al., 2006), and who “test the blockade” using opiates early in a course of naltrexone treatment (Sullivan et al., 2007; Carpenter et al., 2009). We, therefore, conducted a secondary analysis of a previously reported placebo-controlled randomized controlled trial of XR-NTX (Krupitsky et al., 2011), examining a range of baseline demographic variables and other clinical characteristics measured at baseline, some of which are indicators of severity of illness to explore the extent to which any of these variables predict better or worse outcome on XR-NTX compared with placebo. Although this was an exploratory analysis, the guiding hypothesis, based on the prior findings with oral naltrexone (Sullivan et al., 2007; Carpenter et al., 2009), was that XR-NTX would be relatively more efficacious among patients with milder severity of opioid dependence and associated problems including medical consequences, HIV, hepatitis C, and chronicity.

METHODS

Participants

The study, described in detail elsewhere (Krupitsky et al., 2011), was conducted at 13 sites in Russia and recruited adults 18 years old and older who met criteria for opioid (primarily heroin) dependence disorder, completed inpatient opioid detoxification (≤ 30 days), and were off opioids for 7 days or more. Patients were volunteers (ie, not under justice system coercion) who had a significant other who would supervise the subject's study compliance. Women of childbearing potential agreed to use contraception during the study. Exclusions included pregnancy or breastfeeding; significant medical conditions; positive naloxone challenge (vital sign elevations or opioid withdrawal symptoms); hepatic failure, past/present history of an AIDS-indicator disease, active hepatitis, and/or liver enzyme elevations 3X or more upper limit of normal; known intolerance and/or hypersensitivity to XR-NTX or its components; active psychosis, bipolar disorder, major depressive disorder with suicidal ideation, or current substance dependence other than opioids or heroin; positive urine test for cocaine/amphetamines/benzodiazepines; alcohol use disorder or dependence; or naltrexone use within the last 6 months. All study sites obtained institutional review board approval, and participants gave written informed consent in accordance with the Helsinki Accords.

Procedures

Patients were randomized to receive either XR-NTX 380 mg or placebo in a 1:1 ratio, which was administered within 1 week after detoxification and every 4 weeks through the 24-week study period. Sites also provided 12 biweekly sessions of manualized Individual Drug Counseling from psychologists or psychiatrists (Mercer and Woody, 1999).

Double-blinded treatment was maintained among patients, investigators, staff, and the sponsor by using amber vials and syringes. Different personnel conducted the counseling than the data collection. Treatment was offered to patients at no expense and upon completion, patients were offered 12 months of open-label XR-NTX treatment. Patients were not permitted to be prescribed naltrexone, opioids, antipsychotics, anticonvulsants, antidepressants, and anxiolytics; however, they could receive stable dosing of anticonvulsants for seizure disorder treatment and short-acting PRN insomnia medications but not to treat symptoms of withdrawal. An emergency treatment plan for pain management included the use of nonsteroidal anti-inflammatory drugs, regional analgesia, conscious sedation with a benzodiazepine, or general anesthesia.

Assessments

Abstinence assessments were conducted weekly over 24 weeks. Confirmed abstinence was defined as a negative urine drug test for morphine and methadone and no self-reported opioid use on the timeline follow-back survey. Opioid urine drug testing (immunochemistry-based 1-step in vitro tests) was performed for morphine and methadone concentrations 300 ng/mL or more. The timeline follow-back

survey uses calendars and daily recall of substance use on specific days to record quantity or frequency of opioid use (Sobell and Sobell, 1992). Omission of either of these criteria resulted in failure to confirm abstinence for the week.

Patient-reported outcome questionnaires were administered by the study investigators at baseline and at week 24. Assessments included the:

- Addiction Severity Index interview that evaluates 7 variables (medical status, employment and support, drug use, alcohol use, legal status, family/social status, and psychiatric status) with scores normalized from 0 to 1 and higher scores indicating greater problem severity (McLellan et al., 1992).
- Medical Outcomes Study SF-36v2 (SF-36) Health Survey questionnaire mental health summary score (emotional well-being, role limitations due to emotional problems, social functioning, and vitality) and physical health summary scores (physical functioning, role limitations due to physical health problems, pain, general health perceptions) with scores ranging from 1 to 100 and higher scores indicating better health (Ware et al., 2000).
- Revised Clinical Global Impression-Severity (CGI-S) scale is a validated 7-point rating of the patient's illness ranging from "1" (normal, not at all) to "7" (extremely ill) as determined by the investigator (Guy, 1976).
- EuroQol Group Health Outcome Measure (EQ-5D) is a quantitative measure of general health encompassing 5 levels—no problems, slight problems, moderate problems, severe problems, and extreme problems with scores ranging from states worse than dead (<0) to 1 (full health), anchoring dead at 0 (EuroQol Group, 1990).
- Craving was assessed each week using a self-report Visual Analogue Scale (VAS) of "need for opioids" (scale: 0-100, ie, "not at all" to "very much so") (Krupitsky et al., 2004).
- HIV was assessed at baseline and liver enzymes were assessed at baseline and 24 weeks.

Data Analysis

The principal outcome was a dichotomous response measure, namely whether or not a patient achieved at least 90% abstinent weeks during the 24-week trial. This is an indicator of good clinical response because it reflects patients who were both retained in treatment (because patients had to be present to give a urine) and predominantly abstinent across the 24-week trial. To explore baseline variables as predictors of outcome and moderators of the effect of medication treatment (XR-NTX vs placebo), a series of logistic regression models were fit for each moderator, modeling the dichotomous response variable as a function of treatment, the various baseline variables (ie, main effect term), and the baseline-by-treatment interaction. Patients meeting the criterion of good clinical response were disaggregated by treatment condition and examined by CGI-S dichotomized into lower severity (scores 1 to 4: normal, borderline, mildly, and moderately ill) and higher severity (scores: 5 through 7: markedly, severely, and among the most ill) and HIV serostatus on an exploratory basis. All analyses are based on intent-to-treat, that is, including all randomized patients who received at least 1 dose of study drug. Alpha level for predictors or interactions was $P < 0.05$, with

no correction for multiple comparisons in this exploratory analysis.

RESULTS

Characteristics of Patients at Baseline

Table 1 displays the baseline characteristics of the sample stratified by responder status, which was predominantly male, white, and relatively young (with a mean age of 29.6 years). They had an average of 10 years duration of opioid dependence. Of this sample, 90% or more were sero-positive for hepatitis C, and 40% or more were HIV+. At baseline, more than 78% of patients in both clinical outcome groups reported injection of heroin in the preceding 30 days, with 10% to 25% using illicit methadone, or prescription narcotics. In addition to these indicators of baseline severity, the Addiction Severity Index Drug Use Composite Score for the overall sample at baseline was 0.242, SF-36 Mental Component Summary Score was 35.2 (1.5 standard deviations below Russian and US population norms), and CGI-S ratings found 79% to be moderately to severely ill. After a mean of 18 days of inpatient hospital detoxification, craving was still measurable at 20 on a scale of 0 to 100. As previously published, the primary outcome analysis showed that, compared with placebo, XR-NTX increased the proportion of weeks abstinent from opioids and reduced craving for opioids (Krupitsky et al., 2011).

Overall Treatment Response

The criterion for good clinical response ($\geq 90\%$ urine-confirmed abstinent weeks over the 24 weeks of the trial) was achieved by 51.6% (65/126) of patients on XR-NTX, compared with 31.5% (39/124) on placebo (χ^2 (1 df); $P \leq 0.002$), supporting the efficacy of XR-NTX in the sample as a whole, consistent with the previously published findings (Krupitsky et al., 2011).

Patient Characteristics as Moderators of Treatment Response

A series of logistic regression models were fit, 1 for each baseline moderator variable, modeling good clinical response as a function of treatment (XR-NTX vs placebo), the baseline moderator variable, and moderator by treatment interaction. None of the main effects baseline variables was significant, with the exception of CGI-S, where there was a main effect ($P = 0.02$) in the direction of greater severity being associated with a lower rate of Good Clinical Response. None of the moderator by treatment interactions was significant (all were $P > 0.05$). To explore whether trends in the data fell in the predicted direction (variables indicative of higher severity associated with less effectiveness of XR-NTX), we examined descriptively the relationships between baseline variables, treatment, and good clinical response for baseline variables with interaction terms with $P < 0.15$. The treatment by CGI-S interaction missed significance ($P = 0.09$). Figure 1 shows the proportion of patients with good clinical response, disaggregated by lower (CGI-S score 1-4) versus higher (CGI-S score 5-7) severity and by treatment (XR-NTX vs placebo). As can be seen in the figure, the main effect seems to be driven by the placebo group response, in which patients with worse baseline

TABLE 1. Baseline Demographics by Clinical Response Classification

Variables	Clinical Response Classification					
	≥90% Urine-Confirmed Abstinent Weeks (N = 103)			<90% Urine-Confirmed Abstinent Weeks (N = 147)		
	Mean ±SD/ Number (%)	Median	Range	Mean ±SD/ Number (%)	Median	Range
Demographics						
Age (y)	29.2 ± 4.4	29	21-52	29.8 ± 4.1	30	21-45
Sex						
Male	95 (92.2%)			125 (85.0%)		
Female	8 (7.8%)			22 (15.0%)		
Marital status (married)	23 (22.3%)			32 (21.8%)		
Living arrangement (alone vs with family)	4 (3.9%)			6 (4.1%)		
Addiction severity						
Addiction Severity Index (ASI)						
Medical	0.296 ± 0.264	0.278	0.00-0.92	0.267 ± 0.245	0.250	0.00-0.89
Employment	0.709 ± 0.301	0.750	0.04-1.00	0.756 ± 0.254	0.750	0.06-1.00
Alcohol use	0.099 ± 0.111	0.083	0.00-0.63	0.115 ± 0.135	0.084	0.00-0.87
Drug use	0.245 ± 0.074	0.259	0.05-0.40	0.24 ± 0.077	0.254	0.02-0.43
Legal status	0.085 ± 0.107	0.033	0.00-0.45	0.082 ± 0.11	0.000	0.00-0.45
Family/social	0.301 ± 0.215	0.253	0.00-0.89	0.312 ± 0.197	0.322	0.00-0.90
Psychiatric	0.15 ± 0.181	0.045	0.00-0.80	0.119 ± 0.153	0.045	0.00-0.64
Clinical Global Impression-Severity (CGI-S)						
Lower severity (score: 1 to 4)	82 (79.6%)			100 (68.0%)		
Higher severity (score: 5-7)	20 (19.4%)			43 (29.3%)		
Missing	1 (1.0%)			4 (2.7%)		
Opioid dependence duration (y)	8.9 ± 3.9	10	1-23	10 ± 4.4	10	1-26
Age at onset of opioid dependence	20.3 ± 4.1	19	12-37	19.8 ± 4.3	19	12-33
Methadone use in 30 d prebaseline	10 (9.8%)			19 (12.9%)		
Days inpatient detox before study entry	16.7 ± 7.6	15	6-56	18.4 ± 7.7	17	5-67
Craving—at baseline	18.1 ± 20.3	10	0-85	21.3 ± 25.5	10	0-98
Mental and physical health						
SF-36						
Physical component	50.6 ± 6.2	50.7	34.1-62.9	50.5 ± 5.4	50.6	35.8-62.5
Mental component	35.7 ± 10.3	36.8	12.5-58.2	34.8 ± 10.7	35.3	5.2-59.7
EQ-5D						
Self-care						
No problems with self-care	96 (93.2%)			136 (93.2%)		
Mobility						
No problems walking about	85 (82.5%)			120 (82.2%)		
Usual activities						
No problems performing my usual activities	62 (60.2%)			90 (61.6%)		
Pain/discomfort						
No pain or discomfort	56 (54.4%)			86 (58.9%)		
Anxiety/depression						
Moderately anxious/depressed	59 (57.3%)			84 (57.5%)		
HIV sero-positive	40 (38.8%)			66 (44.9%)		

severity were less likely to have a good outcome with counseling plus placebo. Extended-release naltrexone seems to show a similar benefit in both the lower and higher severity groups, which is in the opposite direction from what was hypothesized. Four other variables (HIV serostatus, SF-36 Mental Component, EQ-5D Health subscale, and baseline craving) yielded interaction terms that approached significance ($0.05 < P < 0.15$). Examination of the data similarly showed the nonsignificant trends in the direction of greater difference between XR-NTX and placebo among HIV positive patients (Fig. 1) and those with greater severity on the other variables (data not shown).

DISCUSSION

The previously reported pivotal trial of XR-NTX in preventing relapse among opioid-dependent patients (Krupitsky

et al., 2011) provided an opportunity to examine the efficacy of this once-monthly μ -opioid antagonist formulation in important populations (eg, HIV+ patients) and to examine whether other patient characteristics may moderate the therapeutic effect of XR-NTX for opioid dependence. The traditional consensus on naltrexone as a treatment for opioid dependence, stemming from years of experience with oral naltrexone, has been that oral naltrexone is a niche treatment, effective mainly for a narrow range of good prognosis patients, such as professionals with high motivation and good social supports or patients supported with intensive behavioral treatments reinforcing adherence (Preston et al., 1999; Carroll et al., 2001; Nunes et al., 2006). The monthly injection formulation, however, was called for to address the poor adherence that has plagued oral naltrexone, which requires adherence with daily pill taking (Willette, 1976). The analysis described here

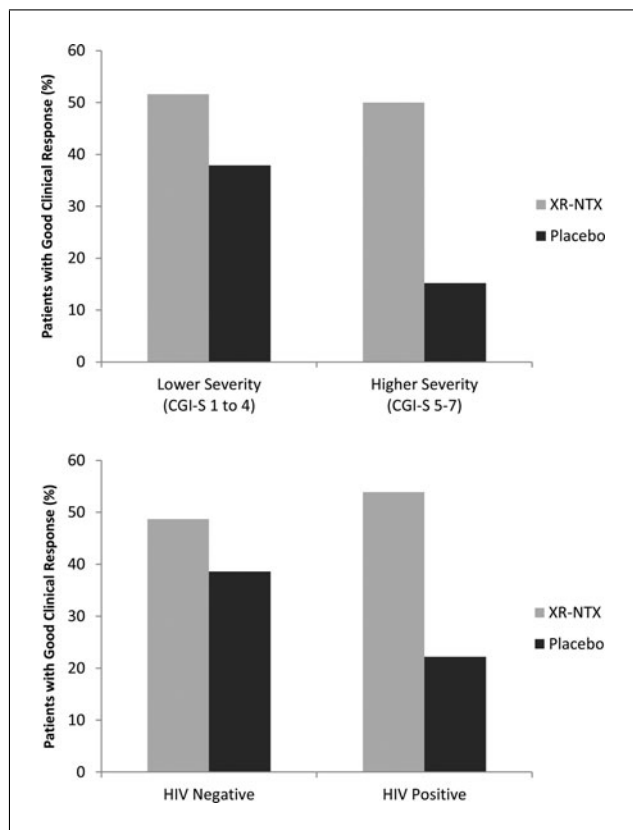


FIGURE 1. Good clinical response (1) stratified by baseline Clinical Global Impression-Severity of illness and HIV serostatus. Top panel: Clinical Global Impression-Severity (CGI-S) (2) is dichotomized into lower severity (scores 1-4: normal, borderline, mildly, and moderately ill) and higher severity (scores: 5 through 7: markedly, severely, and among the most ill). Bottom panel: HIV serostatus (positive vs negative). (1) Good Clinical Response is defined as 90% or more urine-confirmed abstinent weeks over the 24 weeks of the trial. (2) The main effect of baseline CGI-S is significant ($P = 0.02$); the baseline CGI-S by treatment interaction is not significant ($P = 0.09$). (3) Neither the main effect of baseline HIV serostatus ($P = 0.06$) nor the HIV serostatus by treatment interaction ($P = 0.07$) is significant. Values from 250 opioid-dependent patients who entered a 24-week randomized, placebo-controlled trial of extended-release naltrexone (XR-NTX) versus placebo.

therefore examined XR-NTX across 25 demographic and clinical severity variables.

There were no significant interactions between treatment assignment and any of the baseline variables. Thus, while our guiding hypothesis was that XR-NTX would be more efficacious for patients with lower severity of illness, there was no evidence of such patient-treatment matching effects in the present data. It is possible that there are moderator variables exerting smaller effects, which were not detected with the present sample size.

We did examine descriptively the observed proportions of patients achieving good clinical response for baseline variables for which the baseline by treatment interaction terms approached significance ($0.05 < P < 0.15$), which included

CGI-S (Fig. 1) and HIV serostatus (Fig. 1), among others. We did this to explore whether the trends fell in the direction of the oral naltrexone legacy hypothesis (greater naltrexone effect among patients with lower severity at baseline), but the trends for XR-NTX were, if anything, independent of baseline patient severity, that is, with XR-NTX, patients with high baseline severity had a rate of good clinical outcome that was similar to those with low baseline severity. Again, it must be emphasized the interactions were not significant, and these descriptive data are of mainly heuristic interest for planning future research.

The study has limitations, first of which is the post hoc predictors design. The study was not powered to detect subgroup differences. Future studies attempting to delineate patient-treatment matching factors should probably plan for larger sample sizes. The large number of analyses creates the opportunity for inflated type I error. Another limitation is that the summary outcome variable examined in this analysis (percentage of patients who achieved $\geq 90\%$ confirmed abstinent weeks) assumes that dropouts are not abstinent. This is an imputation, but it seems reasonable, given that a typical failure mode in the treatment of opioid dependence is dropout, concurrent with relapse.

The study was conducted in Russia, and replications in other nations and cultural settings are needed. Additional studies have emerged on the effectiveness of XR-NTX across a broad range of patient populations (Baser et al., 2011; Bigelow et al., 2012; DeFulio et al., 2012; Crevecoeur-MacPhail et al., 2014); these and future studies should examine the interactions between patient characteristics and outcome. One important feature of the Russian clinical settings is the availability of long hospital stays for detoxification and stabilization. The patients in this trial were detoxified without use of opioid agonists and were in the hospital for an average of 18 (standard deviation = 8) days before starting XR-NTX. This differs from typical treatment settings in the United States, for example, where hospitalizations for opioid detoxification typically last for 1 week or less, and opioid tapers with methadone or buprenorphine are typically used to minimize withdrawal symptoms. Level of opioid use before hospital admission, operationalized as self-reported bags of heroin per day, has been shown in such US settings to be associated with lower treatment retention on oral naltrexone (Sullivan et al., 2006; Sullivan et al., 2007; Carpenter et al., 2009). This is likely because starting naltrexone soon after stopping opioids may involve some degree of precipitated withdrawal. Thus, the relatively long duration between last opioid use and XR-NTX induction in this study might explain the lack of adverse prognostic effect of severity on XR-NTX treatment outcome. Again, future studies are needed to examine the relationship between severity and outcome of XR-NTX treatment in clinical settings where detoxification stays are shorter and utilize agonist tapers.

CONCLUSIONS

We hypothesized, based on the aforementioned clinical experience and literature on oral naltrexone, that patient characteristics indicating greater clinical severity would be associated with less effectiveness of XR-NTX versus

placebo. However, the analyses show that none of the baseline variable-by-treatment interactions reached significance. Thus, there is no evidence of patient-treatment matching factors. The results suggest that XR-NTX was effective in promoting abstinence from opioids and preventing relapse after detoxification across 25 different demographic features and clinical severity characteristics. Therefore, in these patients who reported an average of a decade of intravenous heroin dependence, this analysis extends the overall efficacy findings of the multisite, double blind randomized controlled trial (Krupitsky et al., 2011) with the additional finding that XR-NTX demonstrated its benefit versus placebo with patients of both lower and higher severity. The clinical implications of these findings seem to contradict conventional wisdom regarding oral naltrexone in opioid dependence. Also, in the absence of empirical predictors, patient preference may be a reasonable basis for medication selection with clinicians relying on clinical judgment and then observing the patient's clinical response. The findings further suggest the promise of XR-NTX as an addition to the treatment armamentarium for opioid dependence. More research is needed in an effort to delineate patient-treatment matching factors for medication treatments for opioid dependence.

REFERENCES

- Baser O, Chalk M, Fiellin DA, et al. Cost and utilization outcomes of opioid-dependence treatments. *Am J Manag Care* 2011;17(suppl 8):S235–S248.
- Bigelow GE, Preston KL, Schmittner J, et al. Opioid challenge evaluation of blockade by extended-release naltrexone in opioid-abusing adults: dose-effects and time-course. *Drug Alcohol Depend* 2012;123:57–65.
- Birnbaum HG, White AG, Schiller M, et al. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain Med* 2011;12:657–667.
- Carpenter KM, Jiang H, Sullivan MA, et al. Betting on change: modeling transitional probabilities to guide therapy development for opioid dependence. *Psychol Addict Behav* 2009;23:47–55.
- Carroll KM, Ball SA, Nich C, et al. Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence: efficacy of contingency management and significant other involvement. *Arch Gen Psychiatry* 2001;58:755–761.
- Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2006;63:210–218.
- Crevecoeur-MacPhail D. *Whose mu Fared Better? The Effect of Extended Release Naltrexone on Treatment Outcomes for Opioid and Alcohol Users*. Paper presented at: the 2014 Annual Addiction Health Services Research (AHSR) Conference; October 15–17, 2014; Boston, MA.
- DeFulio A, Everly JJ, Leoutsakos JM, et al. Employment-based reinforcement of adherence to an FDA approved extended release formulation of naltrexone in opioid-dependent adults: a randomized controlled trial. *Drug Alcohol Depend* 2012;120:48–54.
- EuroQol Group. EuroQol, a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
- Gastfriend DR. Intramuscular extended-release naltrexone: current evidence. *Ann NY Acad Sci* 2011;1216:144–166.
- Goldstein A. Heroin addiction: neurobiology, pharmacology, and policy. *J Psychoactive Drugs* 1991;23:123–133.
- Guy W. *ECDEU Assessment Manual for Psychopharmacology—Revised*. Rockville, MD: US Department of Health and Human Services, 1976. DHHS Publ No ADM 91-338.
- Hulse GK, Morris N, Arnold-Reed D, et al. Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone. *Arch Gen Psychiatry* 2009;66:1108–1115.
- International Harm Reduction Association. *The Global State of Harm Reduction 2010: Key Issues for Broadening the Response*. London, England: International Harm Reduction Association, 2010.
- Johansson BA, Berglund M, Lindgren A. Efficacy of maintenance treatment with naltrexone for opioid dependence: a meta-analytical review. *Addiction* 2006;101:491–503.
- Kirchmayer U, Davoli M, Verster A. Naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev* 2003;2:CD001333.
- Krupitsky E, Nunes EV, Ling W, et al. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet* 2011;377:1506–1513.
- Krupitsky E, Zvartau E, Woody G. Use of naltrexone to treat opioid addiction in a country in which methadone and buprenorphine are not available. *Curr Psychiatry Rep* 2010;12:448–453.
- Krupitsky EM, Blokhina EA. Long-acting depot formulations of naltrexone for heroin dependence: a review. *Curr Opin Psychiatry* 2010;23:210–214.
- Krupitsky EM, Zvartau EE, Masalov DV, et al. Naltrexone for heroin dependence treatment in St. Petersburg, Russia. *J Subst Abuse Treat* 2004;26:285–294.
- Lobmaier P, Kornor H, Kunoe N, et al. Sustained-release naltrexone for opioid dependence. *Cochrane Database Syst Rev* 2008;2:CD006140.
- Mattick RP, Breen C, Kimber J, et al. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev* 2009;2:CD002209.
- Mattick RP, Kimber J, Breen C, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2003;2:CD002207.
- McLellan AT, Kushner H, Metzger D, et al. The fifth edition of the addiction severity index. *J Subst Abuse Treat* 1992;9:199–213.
- Mercer DE, Woody GE. *Therapy Manuals for Drug Addiction Series. Individual Drug Counseling*. Rockville, MD: National Institutes of Health, US Department of Health and Human Services, 1999.
- Metzger DS, Navaline HA, Woody GE. Assessment of substance abuse: HIV risk assessment battery (RAB). In: Carson-DeWitt R, Macmillan-Thomson G, eds. *Encyclopedia of Drugs, Alcohol, and Addictive Behavior*. New York, NY: Macmillan Reference, 2001.
- Minozzi S, Amato L, Vecchi S, et al. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev* 2011;4:CD001333.
- Nunes EV, Rothenberg JL, Sullivan MA, et al. Behavioral therapy to augment oral naltrexone for opioid dependence: a ceiling on effectiveness? *Am J Drug Alcohol Abuse* 2006;32:503–517.
- Preston KL, Silverman K, Umbricht A, et al. Improvement in naltrexone treatment compliance with contingency management. *Drug Alcohol Depend* 1999;54:127–135.
- Reece AS. Psychosocial and treatment correlates of opiate free success in a clinical review of a naltrexone implant program. *Subst Abuse Treat Prev Policy* 2007;2:35.
- Sobell LC, Sobell MB. Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP, eds. *Measuring Alcohol Consumption: Psychosocial and Biological Methods*. Totowa, NJ: The Humana Press, 1992:41–72.
- Stotts AL, Dorrill CL, Kosten TR. Opioid dependence treatment: options in pharmacotherapy. *Expert Opin Pharmacother* 2009;10:1727–1740.
- Substance Abuse and Mental Health Services Administration. An introduction to extended-release injectable naltrexone for the treatment of people with opioid dependence. *Advisory* 2012;11.
- Sullivan MA, Garawi F, Bisaga A, et al. Management of relapse in naltrexone maintenance for heroin dependence. *Drug Alcohol Depend* 2007;91:289–292.
- Sullivan MA, Rothenberg JL, Vosburg SK, et al. Predictors of retention in naltrexone maintenance for opioid dependence: analysis of a stage I trial. *Am J Addict* 2006;15:150–159.
- Ware JE, Kosinski M, Dewey JE. *How to Score Version Two of the SF-36 Health Survey*. Lincoln, RI: Quality Metric, 2000.
- Willette RE. The development of sustained action preparations of narcotic antagonists. *NIDA Res Monogr* 1976;9:31–34.